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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,489	04/03/2001	Sudhir Agrawal	047508.514 US2 (HYZ-075)	2089
23483	7590	12/27/2005	EXAMINER	
WILMER CUTLER PICKERING HALE AND DORR LLP 60 STATE STREET BOSTON, MA 02109			VIVLEMORE, TRACY ANN	
		ART UNIT	PAPER NUMBER	1635
DATE MAILED: 12/27/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/825,489	AGRAWAL ET AL.	
	Examiner Tracy Vivlemore	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 16 March 2005 and 06 October 2005.
- 2a) This action is **FINAL**.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-48 is/are pending in the application.
- 4a) Of the above claim(s) 3-9, 15-18, 23-29, 35-38 and 41-48 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1, 2, 10-14, 19-22, 30-34, 39 and 40 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 03 April 2001 is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                     | Paper No(s)/Mail Date. _____ .  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|  | 6) <input type="checkbox"/> Other: _____ .                                  |

## **DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection not reiterated in this Action is withdrawn.

### ***Election/Restrictions***

Applicant's remarks regarding the status of the claims following the restriction requirement are acknowledged. Applicant's attention is directed to paragraph 7 of the previous Office Action, where the withdrawal from consideration of claims 3-5 and 23-25 as being non-elected species and claims 15, 16, 35 and 36 as being a non-elected invention is indicated. It is noted that Applicant states that the species of SEQ ID NO: 4 will be examined if SEQ ID NO: 3 is found to be patentable however, sequence restrictions are not species elections; they are restrictions between independent and distinct inventions.

The examiner notes that in claim amendment dated March 16, 2005 the status of claims 3-5 is "original" when it should be "withdrawn". Any future amendments must indicate the proper status of all claims.

### ***Priority***

In view of the decision by the Office of Petitions with regard to the petition filed October 6, 2005, the effective filing date of this application is April 3, 2000.

***Response to arguments- Claim Rejections - 35 USC § 112, enablement***

Claims 1, 2, 10-14, 19-22, 30-34, 39 and 40 remain rejected under 35 U.S.C. 112, first paragraph for the reasons of record set forth in the Office Action mailed September 14, 2004.

Applicant asserts the Examiner has improperly characterized the references cited in the original rejection as supporting lack of enablement and has selectively quoted passages to support the finding of lack of enablement. This is not the case, the references have been considered in their entirety, the quotations are present solely to point out reasons for the finding of lack of enablement. Applicant quotes one of the concluding statements from the reference of Agrawal et al. detailing the progress made in the field of antisense. The examiner agrees that many questions regarding antisense have been answered to a large extent; however, even this assessment of progress is qualified by the clause "if proper design and controls are used". Despite progress in the field, delivery of antisense therapeutics remains an unpredictable art.

The quotation from Jen et al. is not relied upon to apply an improper standard for patentability, but merely to recount the teachings of the prior art. Applicant's remarks regarding the section of Jen et al. regarding efficacy of effect (and the quotation from Scott v. Finney) are acknowledged but do not address delivery of antisense therapeutics.

Applicant asserts there are numerous publications that support enablement of the claimed methods throughout its scope. The examiner acknowledges that the prior art provides some examples of successful use of therapeutic nucleic acids *in vivo*,

however, the successful application of one antisense compound does not provide evidence of predictability of the entire field of antisense.

Applicant quotes a portion of MPEP 2164.02 and asserts this section provides that *in vitro* data provides evidence of *in vivo* methods. Applicant further asserts the specification provides extensive *in vitro* data that provides evidence of *in vivo* enablement. This is not persuasive since the cited section is referring to whether or not *in vitro* data can be considered a working example. It is noted that the quoted MPEP section doesn't state that the existence of *in vitro* data proves *in vivo* enablement.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 10, 19-22, 30, 39, 40 and 49 are rejected under 35 U.S.C. 102(a) as being anticipated by Lu et al. (IDS of 5/16/2002, reference A1)

Claims 1 and 21 are drawn to a method of potentiating or enhancing the toxic effect of a cytotoxin on a cancer cell or sensitizing a resistant cell using an antisense oligonucleotide against the XPA gene in combination with a cytotoxin. Claims 2 and 22 state the method is performed with the cytotoxin cisplatin, claim 10 and 30 state the antisense oligonucleotide is directed to XPA gene, claims 19, 20, 39 and 40 state the

types of cancers targeted, and claim 49 is a generic re-statement of claim 1 wherein the target gene is any gene involved in TCR or NER.

Lu et al. disclose that cisplatin toxicity can be potentiated by combining with antisense oligonucleotides targeted to XPA, a gene involved in NER, in SKBR-3 breast carcinoma cells. Lu et al. thus discloses all limitations of claims 1, 2, 10, 19-22, 30, 39, 40 and 49.

***Response to arguments - Claim Rejections - 35 USC § 102***

Applicant states that in view of the perfected priority date the Lu et al. reference is available only under 102(a) and that because all the authors of the Lu et al. reference are inventors of the instant invention this reference is not by others. This argument is not persuasive because the Lu et al. reference is by others; the reference has four authors while this application has five named inventors.

***Response to arguments - Claim Rejections - 35 USC § 103***

Claims 1, 2, 10, 11, 14, 19-22, 30, 31, 34, 39 and 40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tortora et al. in view of Koberle et al. and Horton et al.

Applicant's arguments filed March 16, 2005 have been fully considered but they are not persuasive. Applicant argues that Tortora et al. and Horton et al. do not teach targeting of the XPA gene with antisense oligonucleotides. Applicant further argues that the reference of Koberle et al. does not teach antisense oligonucleotides at all. Applicant is correct, the references of Tortora et al. and Horton et al. do not teach

antisense oligonucleotides directed to XPA, and Koberle does not teach antisense oligonucleotides, but this rejection is based on the combination of these references and each reference is relied upon for specific teachings. The references of Tortora et al. and Horton et al. provide teachings that antisense oligonucleotides can act synergistically with cytotoxins such as cisplatin and that drug resistance correlates with levels of DNA repair enzymes. Koberle et al. teaches the relationship between a reduced level of XPA and increased sensitivity to cisplatin.

Applicant further argues that the Koberle et al. reference provides no expectation of success in using the claimed method to treat a cancer cell because Koberle et al. teaches that testicular germ cell tumors behave differently from most other forms of metastatic cancer. This argument is not persuasive because the claims are directed to cancer, not metastatic cancer and testicular germ cell tumors are a form of cancer.

Applicant further argues that none of the references applied under 35 USC 103 address the issues raised in the 35 USC 112 enablement rejection. It is noted that this rejection is for scope of enablement and that *in vitro* embodiments of the claimed method have been indicated as enabled. The obviousness rejection is directed to the enabled *in vitro* embodiments.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has

been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore  
Examiner  
Art Unit 1635

TV  
December 19, 2005

  
**J.D. SCHULTZ, Ph.D.  
PATENT EXAMINER**